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REMARKS

Claims 69-80, 83-94, and 123-163 are pending. Claims 81, 82 and 95-122 have been cancelled. New claims 127-163 have been added. Support for the amendments and new claims can be found throughout the application as originally filed. No new matter has been added.

Claim Objections

Claim 117 is objected to because "it depends from claim 159. This appears to be a typographical error." Claim 117 has been cancelled, thereby obviating this objection.

Rejection under 35 U.S.C. §112

Claims 81-122 are rejected under 35 U.S.C. §112, ¶ 1, on the grounds that the specification, which is "enabling for the specific deposited PSMA antibodies E99, J415, J533, and J591, does not reasonably provide enablement for any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies having variant or altered sequences." According to the Examiner, "[t]he specification fails to disclose specific guidance or working examples with regard to epitope mapping, or variations of the specific sequences of the disclosed antibodies." Office Action, page 3. The Examiner goes on to state "[e]pitope mapping and alterations of antibody structure are known to be complex and unpredictable. With regard to claims drawn to antibodies which bind to the epitope bound by antibodies E99, J415, J533, and J591, it would require undue experimentation to select and screen for these antibodies." The Examiner further states that "[t]he specification teaches a competitive binding assay of the antibodies E99, J415, J533, and J591 ..."

Office Action, pages 4-5. The portion of the rejection relating to epitope binding is overcome by canceling claims and adding new claims. The remainder of the rejection is traversed.

Claims 81 and 82 have been cancelled. New independent claim 128, and its dependencies, have been added which are directed to methods of treating, preventing or delaying

development or progression of prostate cancer using antibodies that compete for binding to prostate specific membrane antigen (PSMA) with at least one of the monoclonal antibodies selected from J591, J415, J533 and E99.

The application clearly provides sufficient guidance such that a skilled artisan could make and use the antibodies as currently claimed without undue experimentation. Applicant has taught methods of making anti-PSMA antibodies and methods of testing to determine if they compete for binding with the specified antibodies as required in the claims.

For instance, Example 3 of the application at page 36, line 33 – page 37, line 18, teaches a skilled artisan how to generate antibodies against PSMA. Briefly, female BALB/c mice were immunized peritoneally three times at two week intervals with LNCaP cells, which express high levels of PSMA on the surface. A final booster with cultured fresh prostate epithelial cells was administered, and three days later spleen cells from the immunized mice were fused with SP-2 mouse myeloma cells to form hybridomas. Several rounds of screening followed by subcloning by limiting dilution resulted in the isolation of the monoclonal antibodies disclosed herein.

The claimed antibodies are required to compete with a monoclonal antibody selected from the group of E99, J415, J533 and J591. Each of these four monoclonal antibodies has been deposited and is thus available to one of ordinary skill in the art. A skilled artisan could use art known methods together with the specific antibodies which have been made publicly available to determine if a candidate antibody meets the competition limitation. For example, the artisan could follow the protocol set out in Example 10 of the specification which teaches a competition assay. See, e.g., page 42, line 17 – page 44 line 4 of the present application. Thus, a skilled artisan, following the guidance provided by the application, using routine methods and publicly available reagents, could produce an antibody that competes for binding with any one of J415, J591, J533 and E99 without undue experimentation.

The Examiner further asserts that "the specification fails to disclose specific guidance or working examples with regard to ... variations of the specific sequences of the disclosed antibodies including CDR grafting and engineering of the claimed antibodies." In particular, the Examiner states that:

> [W]ith regard to claims which recite antibodies which minimally contain "binding portions" of various antibody regions (claims 83-122), it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function ... It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of the E99, J415, J533, and J591 antibodies, in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

Applicant respectfully traverses the Examiner's statement regarding the lack of enablement for antibodies having altered or variant sequences. As noted by the Examiner, at the time of the invention, much was known in the art regarding the structure and function of antibodies. The state of the art referred to by the Examiner actually supports enablement. For example, the Examiner discusses the role of heavy and light chains and CDR's in maintaining antibody function. This is in fact guidance for one who would make the antibodies of the invention. A skilled artisan would have been able to make and use a wide variety of antibodies and antigen binding fragments which retain antigen binding capability without undue experimentation.

For example, numerous methods were known in the art for producing functional antibodies or antigen-binding fragments thereof with variant sequences. For instance, various methods for humanizing antibodies produced in mice were known at the time of the invention. To highlight just a few, Queen et al, *Proc Natl Acad Sci U S A.* 1989 Dec;86(24):10029-33, teach antibodies humanized by combining the CDRs of a mouse antibody with human framework and constant regions; EP 0 328 404 teaches replacing the CDRs of human antibodies with those from a mouse; Riechmann et al., *Nature* 1988 Mar 24;332(6162):323-7, teach human antibodies reshaped by introducing the hypervariable regions from a rat monoclonal antibody; EP 0 403 156 teaches "civilized" antibodies created by mutating residues in mouse antibody variable regions to

the human sequence and expressing them with human constant regions. U.S. Patent No. 5,225,539 to Winter et al. discloses methods for producing altered antibodies by replacing the CDRs of a variable region of an Ig with the CDRs from an Ig of different specificity, using recombinant DNA techniques. Thus, in view of the knowledge in the art and the information provided in the present application, a skilled artisan could produce a wide variety of anti-PSMA antibodies without undue experimentation. The use of fragments or portions of antibodies was also known in the art at the time of the invention. See, e.g., page 23 of the present application.

The Examiner further argues that antibodies having other than the specific constellation of CDR's from E99, J415, J591 or J533 would not have the required binding function. Applicant respectfully traverses this portion of the rejection. The Examiner has provided no reason at all to believe that immunization as described in the present application would not produce antibodies with the claimed properties which have CDR's other than those of E99, J415, J533, and J591. Four different antibodies were made and disclosed in the application - - the Examiner provides no scientific basis for believing they are the only ones that could be made when the immunization and selection protocols provided by the Applicant are followed. Thus, the specification teaches one how to make antibodies of the invention other than those recited in the examples. In addition, the specification, together with art-known knowledge, allows one to use antibodies like E99, J415, J533 and J591 to make variants such as CDR grafted or humanized antibodies.

The Examiner cites Panka et al. for the proposition that alterations of a single amino acid residue can alter antigen-binding affinity. First, the claims do not require that all antibodies of the claim have the same affinity as the recited examples. Second, Panka et al. were looking for variants with altered binding properties, and describe the use of two-color FACS for doing so. The variant discovered by Panka et al is a serine-to-arginine mutation in the variable region of the antibody. Such a mutation, which is not considered a conservative mutation, might be expected to have such a result. This does not mean that one of skill in the art would be unable to produce variants of the claimed antibodies with altered sequences that retain the antigen-binding properties of the parent molecule. For instance, it was known that antibody variants made by conservative substitutions or substitutions in specific areas are less likely to affect antigen binding. Humanization, for example, replaces large numbers of donor antibody residues. Thus,

the Panka et al. reference further demonstrates Applicant's point that the knowledge in the art was at a high level. The art such as the CDR grafting and humanization references cited above demonstrate ways in which the art teaches how to make changes which do not destroy affinity.

The Examiner also cites Adair et al. as teaching that "transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product." In fact, Adair et al. teach a protocol for obtaining satisfactory CDR-grafted products regardless of the level of homology between the donor immunoglobulin and acceptor framework, see Adair, p. 6. The portion of Adair relied upon by the Examiner is the background in which a reference, Reichmann et al., is discussed. Adair et al. disclose that after CDR grafting it was found that an additional residue in the humanized antibody needed to be modified to enhance binding affinity. Adair et al. (and other references cited in the background of Adair et al.) then go on to provide protocols for designing humanized antibodies with binding activity. Thus, the Adair et al. reference, like the Panka et al. reference, provides another example of the amount of knowledge there was in the art at the time of filing regarding antibody structure and function.

The claims recite an "antigen binding portion" of an antibody. As admitted by the Examiner, it was well established in the art what portions of an antibody are needed to maintain binding capability. Therefore, given the guidance provided by the specification, the level of skill in the art, the level of knowledge regarding antibody structure and function, and the limitation of the claims to antibodies or antigen-binding portions thereof, it is clear that the claimed antibodies have been fully enabled.

Claims 69-126 are rejected under 35 U.S.C. 112, ¶1, on the grounds that the specification, which is "enabling for a method of ablating or killing prostate cancer cells in vitro, does not reasonably provide enablement for a method of treating, preventing, or delaying development or progression of prostate cancer, including in vivo therapy." The Examiner goes on to state "the specification provides evidence of the ability of the antibodies to target tissues *in vitro* for detection but provides insufficient objective evidence that antibodies to the PSMA extracellular domain, or the antibodies E99, J415, J533, and J591 effectively bind to cancerous prostate epithelial cells *in vivo*" and that the specification "provides insufficient evidence that the

instant antibodies are predictably effective in ablating or killing cells in the in vivo clinical situation."

Applicant respectfully traverses this rejection. The Applicant has begun clinical trials using the antibodies of the invention and has demonstrated that the claimed antibodies against the extracellular domain of PSMA achieve not only effective targeting *in vivo* but also produce significant anti-tumor effects in both animal models and human subjects. Applicant provides herewith Exhibits M-O which demonstrate the feasibility of the claimed methods. For example, Exhibit M reports the use of the anti-PSMA antibody J591 conjugated to a cytotoxin, namely DM1, in a LNCaP tumor xenograft mouse model. This report demonstrates that J591 conjugated with a cytotoxin reduced the size of the tumor xenograft. Exhibit N reports that three patients receiving anti-PSMA antibody J591 conjugated with ^{90}Y or ^{177}Lu demonstrated substantial, significant and sustained decreases in PSA levels. Exhibit O demonstrates the anti-tumor effect of naked unconjugated J591 on decreasing PSA levels. These are just a few of the numerous reports of the successful use of the claimed anti-PSMA antibodies to treat prostate cancer in human subjects. In view of such data, it is clear that the claimed antibodies can be used to effectively treat and prevent the progression or development of prostate cancer in both animal models and human subjects without undue experimentation.

Applicant would also like to address the Examiner's assertion that "[i]ndeed, there is not indication that binding of J591 antibody to live LNCaP cells had any effect on their viability." This is simply not the case. Applicants direct the Examiner's attention to Example 1 at page 32 of the application. In obtaining the antibodies disclosed in the present application, Applicants state that the "supernatant was screened by complement cytotoxicity assays against viable LNCaP cells ... [and] clones which were positive were selected." From this example, antibodies J591, as well as, antibodies J415, J533 and E99 were obtained. Thus, contrary to the Examiner's assertion, it is clear that all four of these antibodies were taught to have a cytotoxic effect on viable LNCaP cells.

The Examiner also rejected the claims as being non-enabled for the prevention of development or progression of prostate cancer. Specifically the Examiner states that

> with regard to claims which recite prevention of prostate cancer, an effective protocol for the prevention of a tumor in a human patient is subject to a number of factors beyond simple administration of a composition comprising a relevant antibody in an acceptable formulation. Demonstrating tumor antigen specificity in vitro cannot alone support the predictability of the method for preventing said tumor growth thorough administration of an antibody which binds that antigen. The establishment and growth of a tumor is subject to variables beyond antigen specificity. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending on factors such as the condition of the host, the type of tumor (rapidly proliferating or slowly proliferating) and the tumor burden....

This rejection is respectfully traversed. Anti-PSMA antibodies are much more than a "relevant antibody" they are antibodies to an antigen present on prostate cells throughout the progression from normal to cancer cell types. Furthermore, the Applicant has shown much more than just *in vitro* specificity. The Applicant has demonstrated that antibodies to the extracellular domain of PSMA bind to prostate cancer cells *in vivo*. The specification teaches that the antibodies of the invention bind prostate cells, see, e.g., experiments where antibodies labeled with radioactive isotopes are administered to a patient and then imaged using routine imaging methods, see, e.g., pp. 25-28. The results of such imaging are illustrated in Exhibit P, attached hereto. Exhibit P demonstrates that ^{111}In-labelled J591 antibodies are capable of localizing to, penetrating into, and binding to prostate cells in sufficient quantities to produce a clear image, indicating the localization of PSMA-expressing prostate cancerous cells. Thus, the antibodies of the invention bind to an antigen present on normal, benign hyperplastic and cancerous prostate cells and they bind *in vivo*. In addition, as demonstrated by the Exhibits M-O, discussed above, Applicants have demonstrated that use of the claimed antibodies results decreases in PSA levels in human patients. Prostate cancer provides a particular opportunity for prevention. It is often preceded by a precancerous condition and there is often a long lag period between the precancerous condition and cancer. So there is warning of its impending onset and an opportunity to treat. A well known condition, benign hyperplastic proliferation of the prostate,

can precede a cancerous state. Administration of anti-PSMA antibodies could begin during the stage prior to cancer, to prevent or delay development or progression. See, e.g., page 13, lines 11-33, of the specification which teaches treatment of benign states (by killing or ablating normal or benign hyperplastic prostate cells) and page 29, lines 11-15 which discloses prophylactic treatment to prevent cancer. This clearly demonstrates that the claimed antibodies can be used to prevent the progression and development of prostate cancer.

In light of all the evidence provided above, it is clear that one of ordinary skill in the art would be fully enabled to successfully practice the methods as claimed.

For these reasons, Applicant respectfully submits that the rejection under 35 U.S.C. § 112 ¶ 1 should be withdrawn, and the claims passed to allowance without delay.

Rejection Under 35 U.S.C. §102(e)

Claims 69-70, 77-78, 95, and 97-100 are rejected under 35 U.S.C. §102(e) "as being anticipated by Murphy et al., US Patent 6,150,508." In particular, the Examiner states that "Murphy et al. ... teaches a method of treating prostate cancer tissue comprising providing an antibody or antigen binding portion thereof which binds to the extracellular domain of prostate specific membrane antigen, and administering it to a patient in need thereof to treat primary or metastatic prostate cancer." The Examiner goes on to state that "[a]lthough Murphy et al. ... does not explicitly recite that the patient is human, it is implicit in the disclosure, which discusses assays of human fluids, humanized antibodies and tests the antibodies on a human prostate epithelial cancer cell line (LNCaP), and thus the antibodies would function in humans and would bind to prostate epithelial cells."

The Applicant respectfully traverses this rejection. As discussed below, Murphy et al. is removed as prior art in light of the Declaration of Neil Bander, M.D. Under 37 CFR 1.131 (hereafter referred to as "the Bander declaration"), submitted herewith.

Murphy et al is not available as prior art against the present application because Applicant conceived the claimed invention prior to the priority date of the Murphy et al patent and diligently reduced it to practice. In particular, Murphy et al. has a priority date of March 25,

1996. As stated in the Bander declaration, Applicant conceived the claimed invention to practice prior to the priority date of the Murphy et al. patent and was diligent in reducing it to practice. Therefore, Murphy et al is not available as prior art against the present claims.

Applicant respectfully requests that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §103

Claims 69-78 and 95-126 are rejected under 35 U.S.C. §103 "as being unpatentable over Murphy et al., US Patent 6,150,508." In particular, the Examiner states that

> Murphy fails to teach the specific techniques and antibody characteristics which are recited in the dependent claims ...These specific techniques and antibody characteristics are well known in the art. ... Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the treatments taught in Murphy et al., US Patent 6,150,508, with art known techniques for therapy exemplified above and one would have been motivated to do so because these techniques are art recognized equivalents and variations for diagnosis and therapy.

The Applicant respectfully traverses this rejection. As discussed above, Murphy et al. is removed as prior art in light of the Declaration of Neil Bander, M.D. Under 37 CFR 1.131. Therefore, Applicant respectfully request that the Examiner withdraw this rejection.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed are a check for excess claim fees and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 10/25/02

Laurie Butler Lawrence
Reg. No. 46,593

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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Version with markings to show changes made

In the claims:

Claims 81, 82 and 95-122 have been cancelled.

Claims 77 and 126 have been amended as follows:

77. [Amended] A method according to claim 69, wherein the antibody or antigen binding portion binds live cells [and/or wherein the antibody is an IgG].

126. [Amended] A method of treating, preventing, or delaying development or progression of [metastatic] prostate cancer comprising:

providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, wherein the antibody is bound to a cytotoxic drug of bacterial origin; and

administering the antibody or antigen binding portion thereof to a subject in need of treatment under conditions effective to treat, prevent, or delay the development or progression of [metastatic] prostate cancer.

New claims 127-163 have been added as follows:

127. [New] A method of treating, preventing, or delaying development or progression of prostate cancer comprising:

providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, wherein the antibody is bound to a cytotoxic drug of plant origin; and

administering the antibody or antigen binding portion thereof to a subject in need of treatment under conditions effective to treat, prevent, or delay the development or progression of prostate cancer.

128. [New] A method of treating, preventing, or delaying development or progression of

prostate cancer, comprising:

providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen with a monoclonal antibody selected from the group consisting of J591, J415, J533, and E99;

administering the antibody or antigen binding portion thereof to a subject in need of treatment under conditions effective to treat, prevent, or delay the development or progression of prostate cancer.

129. [New] A method according to claim 128, wherein the antibody or antigen binding portion thereof competes for binding to prostate specific membrane antigen with monoclonal antibody J591.

130. [New] A method according to claim 128, wherein the antibody or antigen binding portion thereof competes for binding to prostate specific membrane antigen with monoclonal antibody J415.

131. [New] A method according to claim 128, wherein the antibody or antigen binding portion thereof binds to live cells.

132. [New] A method according to claim 69, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence selected from the group consisting of an amino acid sequence of the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109, and an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit no. HB-12109.

133. [New] A method according to claim 69, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence of the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109, and an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit no. HB-12109.

134. [New] A method according to claim 69, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of a nucleic acid sequence which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109, and a nucleic acid sequence which encodes the variable light chain produced by the hybridoma having ATCC deposit no. HB-12109.

135. [New] A method according to claim 69, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109 and an antigen binding portion of an amino acid sequence encoded by a nucleic acid which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109.

136. [New] A method according to claim 69, 83, 89, or 128, wherein the antibody is a monoclonal antibody.

137. [New] A method according to claim 69, 83, 89, or 128, wherein the antibody or antigen binding portion thereof is internalized with the prostate specific membrane antigen.

138. [New] A method according to claim 69, 83, 89, or 128, wherein the antibody or antigen binding portion thereof is selected from the group consisting of a Fab fragment, a F(ab')2 fragment, and a Fv fragment.

139. [New] A method according to claim 69, 83, 89, or 128, wherein the antibody or antigen binding portion thereof further comprises a cytotoxic drug.

140. [New] A method according to claim 69, 83, 89, or 128, wherein the cytotoxic drug is selected from the group consisting of a therapeutic drug, a compound emitting radiation,

molecules of plant, fungal, or bacterial origin, biological proteins, and mixtures thereof.

141. [New] A method according to claim 140, wherein the cytotoxic drug is a compound emitting radiation.

142. [New] A method according to claim 141, wherein the compound emitting radiation is an alpha-emitter.

143. [New] A method according to claim 142, wherein the alpha-emitter is selected from the group consisting of ^{212}Bi, ^{213}Bi, and ^{211}At.

144. [New] A method according to claim 141, wherein the compound emitting radiation is a beta-emitter.

145. [New] A method according to claim 144, wherein the beta-emitter is ^{186}Re.

146. [New] A method according to claim 144, wherein the beta-emitter is ^{90}Y.

147. [New] A method according to claim 141, wherein the compound emitting radiation is a gamma-emitter.

148. [New] A method according to claim 147, wherein the gamma-emitter is ^{131}I.

149. [New] A method according to claim 141, wherein the compound emitting radiation is a beta- and gamma-emitter.

150. [New] A method according to claim 140, wherein the cytotoxic drug is a molecule of bacterial origin.

151. [New] A method according to claim 140, wherein the cytotoxic drug is a molecule

of plant origin.

152. [New] A method according to claim 140, wherein the cytotoxic drug is a biological protein.

153. [New] A method according to claim 69, 83, 89, or 128, wherein the antibody or antigen binding portion thereof further comprises a label.

154. [New] A method according to claim 153, wherein the label is selected from the group consisting of a biologically-active enzyme label, and a radiolabel.

155. [New] A method according to claim 154, wherein the label is a radiolabel selected from the group consisting of ^{111}In, ^{99}mTc, ^{32}P, ^{125}I, ^{131}I, ^{14}C, ^{3}H and ^{188}Rh.

156. [New] A method according to claim 69, 83, 89 or 128, wherein the antibody or antigen binding portion thereof is effective to initiate an endogenous host immune function.

157. [New] A method according to claim 156, wherein the endogenous host immune function is complement-mediated cellular cytotoxicity.

158. [New] A method according to claim 156, wherein the endogenous host immune function is antibody-dependent cellular cytotoxicity.

159. [New] A method according to claim 69, 83, 89, or 128, wherein the antibody or antigen binding portion thereof is in a composition further comprising a pharmaceutically acceptable carrier, excipient, or stabilizer.

160. [New] The method according to claim 69, 83, 89, or 128 wherein the antibody or antigen binding portion thereof is administered in conjunction with a second therapeutic modality.

161. [New] The method according to claim 160, wherein the second therapeutic modality is selected from the group consisting of surgery, radiation, chemotherapy, immunotherapy and hormone replacement.

162. [New] The method according to claim 161, wherein the hormone replacement comprises treatment with estrogen or an anti-androgen agent.

163. [New] The method according to claim 162, wherein the anti-androgen agent is an agent which blocks or inhibits the effects of testosterone. --

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Neil H. Bander
Serial No. : 09/357,704
Filed : July 20, 1999
Title : TREATMENT AND DIAGNOSIS OF PROSTATE CANCER

Art Unit : 1642
Examiner : Gary Nickol

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.131

I, Neil H. Bander, a citizen of the United States, residing at 2 Hemlock Hills, Chappaqua, NY, 10514, hereby declare as follows:

1. I am the inventor of the subject matter disclosed and claimed in the above-referenced United States Patent Application.

2. I am familiar with the present claims of the application, which are directed to a method of treating, preventing, or delaying development or progression of prostate cancer in a subject.

3. Prior to March 25, 1996, I had conceived my invention as described and claimed in the above-identified application in this country, a NAFTA country or WTO country, and had diligently reduced the invention to practice, as evidenced below.

4. I submit herewith Exhibits A-L, evidence showing conception of the claimed invention prior to the March 25, 1996.

Prior to March 25, 1996, I had conceived of using monoclonal antibodies in the treatment of prostate cancer in humans.

Exhibit A shows an excerpt from a document describing my research on antibodies and their use in cancer that I wrote prior to March 25, 1996. The document dates, dates within the text of the document, and the name of the individual to whom the document is addressed, have been redacted in the excerpt provided in Exhibit A. The document clearly demonstrates that I was actively pursuing monoclonal antibodies for clinical use in prostate cancer.

As indicated in that document, my laboratory had been testing several monoclonal antibodies for their ability to bind to live LNCaP cells, a human prostate cancer model cell line. Several of the antibodies I had already characterized had demonstrated excellent potential, in that they were able to lyse LNCaP cells *in vitro* in the presence of human serum as a source of complement.

I had demonstrated that the antibodies localized to prostate cancer and sites of metastatic disease (in the lymph nodes and liver). More importantly, I had demonstrated that administration of these antibodies to human subjects resulted in treatment and prevention of prostate cancer. For example, I demonstrated that decreased PSA levels were seen upon administration of these antibodies to human subjects, and that there were no signs of relapse seen in these subjects. All of this is shown in Exhibit A. Exhibit A does not discuss the specific antibodies of the invention. In connection with the work described in Exhibit A, I characterized other monoclonal antibodies including the antibodies of the invention. This is shown in Exhibits B-L below.

Exhibit B, is a tag from a mouse cage in my (Dr. Bander's) laboratory indicating that mice immunized with LNCaP cells as part of "Fusion E" experiments were received, immunized, and given a final booster. Dates on the tag have been redacted. The dates show the work was done prior to March 25, 1996.

Exhibits C-L discussed below all show pages from notebooks from my (Dr. Bander's) laboratory. The date on each of the pages is redacted. Each page is dated prior to March 25, 1996.

Exhibit C is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry shows rosette and cytotoxicity studies of the fusion E antibodies including monoclonal antibody E99 (which is an antibody of the invention), and demonstrates that monoclonal antibody E99 binds to LNCaP cells, a human prostate cancer cell line.

Exhibit D is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that E99 binds renal tubules very weakly, and binds prostate cancer cells strongly.

Exhibit E is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that E99 binds to benign hyperplastic prostate tissue obtained from various human patients. E99 was detected using a fluorescein label.

Exhibit F is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that E99 is an IgG_3 class antibody.

Exhibit G is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that the E99 antibody is capable of lysing PSMA-expressing LNCaP cells, but not PSMA-negative PC3 and Du145 cells.

Exhibit H is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that E99 binds strongly to prostate cancer and benign hyperplastic prostate tissues from human patients, binds normal kidney proximal tubules weakly, and does not bind at all to normal liver, lung, pancreas, testis, esophagus, uterus, small bowel, stomach, thyroid, or spleen.

Exhibit I is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that E99, J415 and J533 (all of which are antibodies of the invention) bind kidney proximal tubules and LNCaP prostate cancer cells, a human prostate cancer cell line, but do not bind normal colon.

Exhibit J is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that E99 and J591 (both of which are antibodies of the invention) bind kidney proximal tubules and LNCaP prostate cancer cells, but do not bind normal colon.

Exhibit K is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates that the J415, J533, and E99 antibodies bind weakly to proximal tubule cells of the normal kidney, and bind benign hyperplastic prostate and cancerous prostate tissue from human patients, and that the J415 and J533 antibodies do not bind at all to normal liver, small intestine, or lung.

Exhibit L is an entry from a laboratory notebook in my (Dr. Bander's) laboratory. This entry demonstrates monoclonal antibodies including E99, J415, J533 and J591 bind to prostate cancer tissue from a number of individuals.

5. Exhibit A demonstrates that I had conceived of using monoclonal antibodies in the treatment and prevention of prostate cancer and Exhibits B-L demonstrate that antibodies which bind PSMA and recognize benign hyperplastic, and cancerous prostate cells from human patients were produced for clinical use in human subjects prior to March 25, 1996. In sum, I submit evidence herewith that shows conception of the claimed invention prior to March 25, 1996.

6. Very shortly after March 25, 1996, namely, May 6, 1996, just a little more than 5 weeks later, the claimed methods were constructively reduced to practice upon filing of provisional application 60/016,976 from which the above-identified application claims priority.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, under Title 18 § 1001 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

10/7/02
Date

Neil Bander, MD

Exhibit A

[redacted]

Particularly when viewed in the context of the advances in the mAb therapy field in general, the attributes and strengths of mAbs are particularly well-suited to the demands of prostate cancer therapy:

1. mAbs can specifically localize to disseminated tumor sites at levels orders of magnitude higher than normal tissues.

2. Therapeutic efficacy has been proven in tumor types (e.g., colon cancer and NHL) where the clinical setting resembles prostate cancer.

3. mAbs have a number of potential mechanisms of anti-tumor activity including:

    a. the relative radiosensitivity of PCa provides one potential class of cytotoxic agents to specifically deliver to tumor sites by way of mAb.

    b. mAbs can trigger the host's own immune response to tumor.

4. Prostate cancer metastases are small-volume sites (typically measured in microns or mm) ideal for radioisotope or immunotherapy.

5. The availability of established parameters such as PSA and pathological features (e.g., stage, Gleason score, seminal vesicle invasion, positive margins, nodal disease, etc.), provide appropriate indications for adjuvant mAb therapy where such therapy is likely to be most beneficial.

6. Last, but not least, is the fact that mAbs are non-toxic.

[redacted]

We believe that we are well on the way to prove that these advantages are more than just theoretical. We have recently completed our mAb Prost 30 biodistribution study in 15 patients with prostate cancer. Doses ranged from 1.0 to 20.0 mg of mAb. Fourteen of the 15 patients had their prostates *in situ* and were evaluable for localization of Prost 30. In all 14 of these cases, including two with prior radiation therapy, the prostate was successfully imaged. In two cases, patients had known sites of metastatic disease imaged on conventional CT scans: regional lymph nodes (both patients) and liver (1 patient). In these cases, these sites also were successfully imaged with Prost 30. In four cases, after resecting the prostate one week after mAb administration, the prostate specimens were scanned alongside specimens of blood drawn at the time of the resection (see appended representative figure). These studies confirmed specific uptake in the prostate at substantially higher levels than in the blood, and this uptake persists for more than one week. No patient on the trial had any side effects.

Exhibit A (cont)

[redacted]

Having established the ability of the mAb to localize to disseminated sites of disease, more interesting and potentially far more important is the observation that two hormone-refractory patients with progressively rising PSAs prior to entry on the imaging trial responded with substantial (75%) decreases in their PSAs each lasting 10 months after a single 5 mg dose of Prost 30. None of the other patients on the trial are evaluable for response due to receiving other therapy in addition to Prost 30. As the isotope dose used in this biodistribution trial was too low to explain the responses, we believe the responses were due to the mAb triggering an endogenous anti-tumor immune response. Another interesting and provocative observation is that this trial included 6 "high-risk" patients (high PSA ± high Gleason ± high stage) who underwent radical prostatectomy plus Prost 30 treatment. None of these patients have demonstrated signs of relapse (either metastatic disease or (PSA) failure) with a median follow-up of almost 2 years.

[redacted] unconjugated ("naked") Prost 30 in a series of patients evaluable for response. This was to establish the safety of naked antibody-as a prelude to an adjuvant trial similar to that already shown effective in colon cancer -- and to provide a benchmark with which to compare the results of a radiolabeled mAb trial. Doses range from 1.25 mg to 5.0 mg -- the level at which we saw the responses in the earlier trial. Fifteen weeks into this trial we have entered 16 patients. Many of the patients, including some at the lowest dose level, have responded with declines in PSA ranging from 25-55%. It is obviously too early to discuss duration of response. While this data is exceedingly preliminary, it is certainly provocative, particularly as the mAb has no conjugated cytotoxic moiety.

We have also developed in the laboratory a higher affinity Prost 30 mAb which we have designated Prost 130. Prost 130 binds the same antigen as Prost 30, but at a different, and repeated, site. It is possible that these mAbs (Prost 30 and 130) will be additive or synergistic in combination. Two other mAbs we have recently developed, C37 and C219, have demonstrated both prostate specificity (in vitro and in vivo) and the ability to directly lyse LNCaP cells in vitro in the presence of human serum as a source of complement. Furthermore, the cytotoxicity of these mAbs are synergistic when combined in vitro. [redacted] these three mAbs (Prost 130, C37 and C219) have been contracted to an FDA-approved manufacturer for production of clinical grade material for upcoming trials.

[redacted]

Exhibit B

FORMS BY MEDI LAB & LABEL BOX #47 ALBERTSON N Y 11507
1983

Dr Bander [redacted] Invasion E

COST CENTER # 6801

CAGE ID # 92080 RM. # _____

[redacted]

INVESTIGATOR _____ EXT. 65494

SP/STR. BALB/c SEX ♀

DATE REC'D. [redacted] PO # _____

ID # OR #/CAGE _____ VENDOR _____

Dr Lin Peggy

LNCap cell 6×10^6/per mouse i.p

date [redacted]

Invasion E date [redacted] i.p

date [redacted] i.p

ANIMAL MAINTENANCE

CHARGES TO C.C. _____

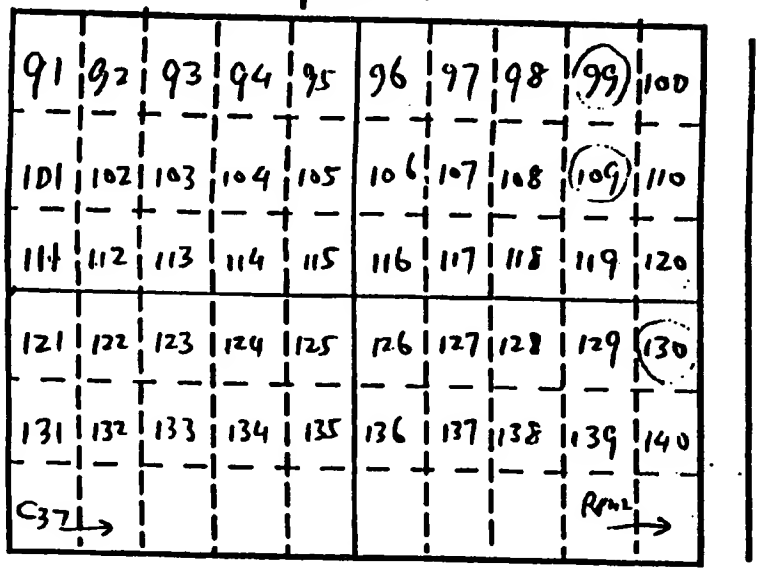
FUND# _____

PROTOCOL# _____

final bleeder : [redacted]

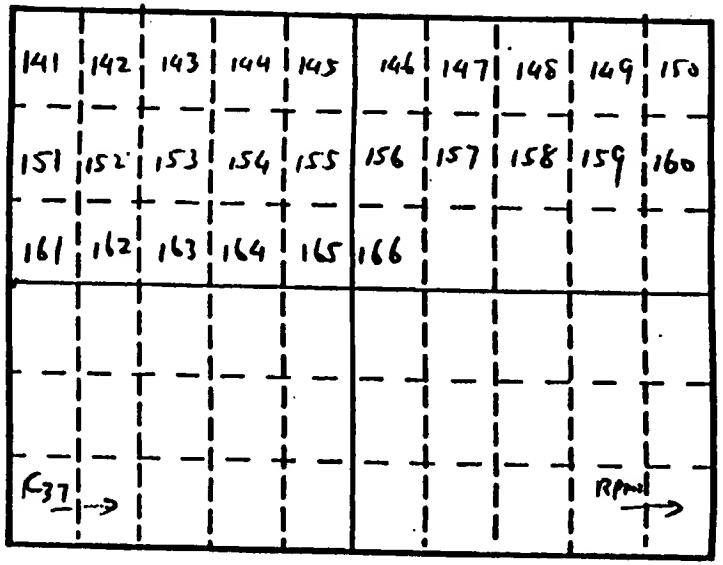
cytotoxicity for: LNCap

plate 1



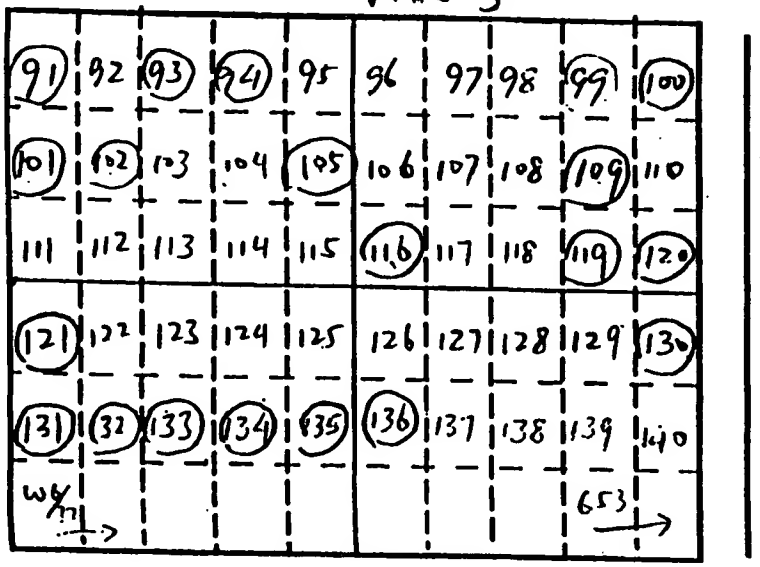
Fusion E

plate 2



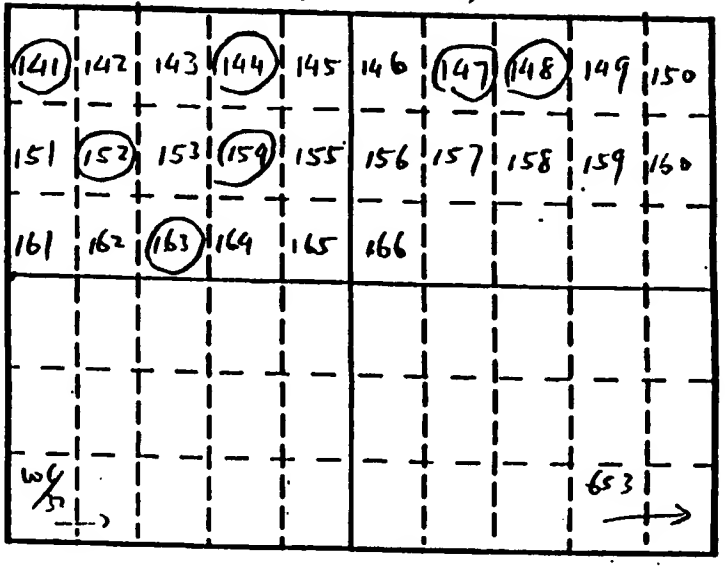
Rosetta Test for LNCap

Plate 3



Fusion E

Plate 4



Terasaki Plate

Exhibit C

EXHIBIT D

[redacted]

Side	Section	MoAb	Result		
1	NK, N colon, Pca	E 91	+	+	+
2	(Kortrey)	E 93	+	+	+
3		E 94	+	+	+
✓ 4		E 99	tube (+)	−	+
5		E 100	−	−	−
6		E 101	+	+	+
7		E 102	−	−	−
8		E 105	+	+	+
9		E 109	+	+	+
10		E 116	−	+	+
✡ VII		E 119	−	−	+
12		E 120	+	+	+
13		E 121	+	−	+
14		E 130	+	+	+
15		E 131	+	+	+
16		E 132	+	+	+
17		E 133	+	+	+
18		E 134	+	+	+
19		E 135	−	−	−
20		E 136	+	+	+
21		E 141	+	+	+
22		E 144	+	+	+
23		E 147	+	+	+
24		E 148	−	−	−
25		E 152	+	+	+
26		E 154	+	+	+
27		E 163	−	−	−
28		Fsi $^{MC}/_{12}$ Pan	+	+	+

Exhibit E

[redacted]

Slide	Section	MoAb		Result	
1	BPH (Friedlander)	C37 ascite 1:100	C219 ascite 1:100	epith — stromal +	epith — stroma
2	"	F27	Eqq		—
3	"	653	P410	—	+
4	"	C37 ascite 1:100	C219 ascite 1:100	—	—
5	"	E27	Eqq	—	—
6	"	653	P410	—	+
7	BPH (Rodriguez, J)	C37 ascite 1:100	C219 ascite 1:100	epith — stromal +	epith + stromal ±
8		E27	Eqq	+	+
9		653	P410	—	+
10		C37 ascite 1:100	C219 ascite 1:100	—	+
11		E27	Eqq	+	weak +
12		653	P410	—	+
13	BPH (CHAN, M.Y.)	C37 ascite 1:100	C219 ascite 1:100	epith — stromal +	epith — stroma ±
14		E27	Eqq	—	+
15		653	P410	—	+
16		C37 ascite 1:100	C219 ascite 1:100	—	—
17		E27	Eqq	—	—
18		653	P410	—	+
19	Bph (Deese, F)	C37 ascite 1:100	C219 ascite 1:100	epith — stromal +	epith + stromal +
20		E27	Eqq	+	+
21		653	P410	—	+
22		C37 ascite 1:100	C219 ascite 1:100	—	+
23		E27	Eqq	+	+
24		653	P410	—	+

FITC-RAMG (slides 4–6)

FITC-RAMG (slides 10–11)

FITC-RAMG (slides 16–18)

FITC-RAMG (slides 22–23)

Exhibit F

Exhibit F (cont'd)

[redacted]

plate 1 15 min

		1 IgG1	2 IgG2a	3 IgG2b	4 IgG3	5 IgM	6 IgG1	7 IgG2a	8 IgG2b	9 IgG3	10 IgM	15min plate 1	
E27	F	+0.22	+0.21	+0.18	+0.34	+1.41	+0.23	+0.21	+0.17	+0.92	+0.58	E99	F
	E	+0.23	+0.22	+0.17	+0.30	+1.37	+0.26	+0.22	+0.18	+1.11	+0.51		E
E119	D	+0.94	+0.19	+0.19	+0.35	+1.39	+1.00	+0.71	+0.31	+0.31	+1.41	E202	D
	C	+0.85	+0.21	+0.20	+0.32	+1.41	+0.95	+0.23	+0.30	+0.40	+1.47		C
653	B	+0.21	+0.17	+0.18	+0.23	+0.26	+0.09	+0.10	+0.10	+0.15	+0.11		B
	A	+0.18	+0.17	+0.13	+0.26	+0.30	+0.09	+0.10	+0.10	+0.13	+0.10		A

plate 2 15 min

		1 IgG1	2 IgG2a	3 IgG2b	4 IgG3	5 IgM	6 IgG1	7 IgG2a	8 IgG2b	9 IgG3	10 IgM	15min plate 2	
E455	F	+0.30	+0.26	+0.22	+0.36	+1.43	+0.38	+0.26	+0.22	+0.39	+1.41	E1032	F
	E	+0.24	+0.23	+0.21	+0.48	+1.43	+0.43	+0.25	+0.17	+0.35	+1.40		E
C37	D	+0.29	+0.27	+0.20	+0.34	+1.43	+0.30	+0.28	+0.20	+0.32	+1.42	C219	D
	C	+0.28	+0.25	+0.19	+0.34	+1.43	+0.25	+0.23	+0.20	+0.32	+1.40		C
653	B	+0.26	+0.19	+0.14	+0.26	+0.32	+0.10	+0.11	+0.09	+0.12	+0.13		B
	A	+0.24	+0.21	+0.13	+0.27	+0.31	+0.09	+0.12	+0.09	+0.29	+0.09		A

plate 1 60 min

		1 IgG1	2 IgG2a	3 IgG2b	4 IgG3	5 IgM	6 IgG1	7 IgG2a	8 IgG2b	9 IgG3	10 IgM	60min plate 1	
E27	F	+0.48	+0.46	+0.36	+0.81	+1.41	+0.50	+0.46	+0.28	+1.38	+1.19	E99	F
	E	+0.52	+0.46	+0.36	+0.72	+1.43	+0.60	+0.47	+0.32	+1.41	+1.16		E
E119	D	+1.39	+0.41	+0.41	+0.80	+1.43	+1.39	+0.67	+0.52	+0.77	+1.41	E202	D
	C	+1.42	+0.47	+0.42	+0.72	+1.44	+1.35	+0.55	+0.41	+0.75	+1.43		C
653	B	+0.45	+0.33	+0.27	+0.53	+0.61	+0.13	+0.14	+0.14	+0.13	+0.15		B
	A	+0.38	+0.35	+0.24	+0.58	+0.71	+0.12	+0.14	+0.13	+0.20	+0.13		A

plate 2 60 min

		1 IgG1	2 IgG2a	3 IgG2b	4 IgG3	5 IgM	6 IgG1	7 IgG2a	8 IgG2b	9 IgG3	10 IgM	60min	
E455	F	+0.66	+0.56	+0.48	+0.85	+1.41	+0.88	+0.60	+0.44	+0.92	+1.47	E1032	F
	E	+0.56	+0.49	+0.43	+1.04	+1.41	+0.94	+0.54	+0.34	+0.80	+1.45		E
C37	D	+0.66	+0.64	+0.41	+0.79	+1.41	+0.68	+0.63	+0.41	+0.73	+1.43	C219	D
	C	+0.61	+0.54	+0.37	+0.77	+1.44	+0.58	+0.53	+0.42	+0.79	+1.44		C
653	B	+0.55	+0.38	+0.25	+0.55	+0.72	+0.12	+0.15	+0.12	+0.18	+0.20		B
	A	+0.51	+0.42	+0.24	+0.59	+0.69	+0.11	+0.17	+0.10	+0.33	+0.10		A

Exhibit G

Cytotoxicity Test

	E27	Eq9	E119	E202	E485	E1022	C37	C219	653
Pc3	−	−	−	−	−	−	−	−	
	−	−	−	−	−	−	−	−	−
	−	−	−	−	−	−	−	−	−
	−	−	−	−	−	−	−	−	−
	−	−	−	−	−	−	−	−	−
Du145	−	−	−	−	−	−	−	−	−
	−	−	−	−	−	−	−	−	−
LNCap	−	+	−	−	−	−	+	+	−
	−	+	−	−	−	−	+	+	−

Cytotoxicity to LNCap [redacted]

C37	Guinea Pig serum								1:3	1:3
	+ 1:3	+ 1:3	+ 1:4	+ 1:4	+ 1:5	+ 1:5	+ 1:6	+ 1:6	653	653
C219	Guinea Pig serum								1:3	1:3
	+ 1:3	+ 1:3	+ 1:4	+ 1:4	+ 1:5	+ 1:5	+ 1:6	+ 1:6	653	653
C37	Human Serum								1:3	1:3
	+ 1:3	+ 1:3	+ 1:4	+ 1:4	+ 1:5	+ 1:5	+ 1:6	+ 1:6	653	653
C219	Human serum								653	653
	+ 1:3	+ 1:3	+ 1:4	+ 1:4	+ 1:5	+ 1:5	+ 1:6	+ 1:6	n3	n3
New C37	+ 1:1	+ 1:2	+ 1:4	+ 1:8	60% 1:16	1:32	1:64	1:128	653	653
New C219	+ 1:2	80% 1:2	40% 1:4	1:8	1:16	1:32	1:64	1:128	653	653

Terasaki Plate

Exhibit H

[redacted]

	Slide	Section	MoAb		Result	
	1	NK (unsoeld, W),	E27	E99	—	pT weak +
46	2		E202	E455	—	—
	3		653	F31	—	+
	4	Nor liver	E27	E99	—	—
	5	(31-53391)	E202	E455	—	—
35	6		653	WB/32	—	+++
	7	Nor lung (20II)	E27	E99	—	—
41	8		E202	E455	Alveola (-)	Bronchiole Basal (+)
	9		653	WB/32	—	+++
	10	Nor pancreas (271)	E27	E99	++	—
	11		E202	E455	—	—
39	12		653	WB/32	—	++
	13	Nor Testis (259)	E27	E99	—	—
39	14		E202	E455	—	—
	15		653	WB/32	—	connective tissue ++
	16	Pca (WHEELER, G)	E27	E99	heterogen ++	weak +
	17		E202	E455	basal + — ++	basal ++
52	18		653	P410	—	weak +
	19	Pca (...)	E27	E99	heterogen + — ++	+ — ++
	20	Culver	E202	E455	heterogen basal +	heterogen basal + —
	21		653	P410	—	+
	22	BPH (...)	E27	E99	—	+
	23	Chanlwon Sam	E202	E455	heterogen +	heterogen ++
51	24		653	P410	—	++

Exhibit H (con't)

[redacted]

	Slide	Section	Mo Ab			
	1	Esophagus (31-53925)	E27	E99	—	—
6	2		E202	E455	basal +	basal +
	3		653	W6/32	—	+
	4	Nor Uterus (31-52931)	E27	E99	—	—
6	5		E202	E455	—	—
	6		653	W6/32	—	+
	7	small bowel (31-51650)	E27	E99	++ - ++	—
	8		E202	E455	—	—
6	9		653	W6/32	—	+
	10	Stomach (31-53027)	E27	E99	—	—
8	11		E202	E455	section not good	
	12		653	W6/32	+	+
	13	Thyroid (P91-422)	E27	E99	—	—
	14		E202	E455	—	—
11	15		653	W6/32	—	+
	16	Spleen (P91-39)	E27	E99	++?	—
	17		E202	E455	—	—
11	18		653	W6/32	—	+
	19	Pca (Mahoney, w)	E27	E99	retrogen	++
	20		E202	E455	++	++
59	21		653	P910	—	retrogen ++
	22	Pca verclugo, j	E27	E99	—	+ - ++
67	23		E202	E455	retrogen weak +	retrogen +
	24		653	P910	—	+ - ++

Exhibit I

[redacted]

Slide	Section	MoAb	Result		
☆	1 NL, N.C., LNCaP tumor	J-267	+	−	+
	2	J-271	+	+	+
	3	J-284	+	+	+
	4	J-297	+	−	−
	5	J-331	+	+	+
	6	J-377	+	+	+
	7	J-380	+	−	−
	8	J-382	+	+	+
	9	J-385	+	+	+
	10	J-386	−	+	−
	11	J-407	+	+	+
☆	12	J-415	PT+	−	+
	13	J-421	+	+	+
	14	J-437	+	+	+
	15	J-445	+	+	−
	16	J-457	+	+	+
	17	J-472	−	−	−
	18	J-478	−	−	−
	19	J-518	−	−	−
	20	J-525	−	−	−
	21	J-527	+	−	+
☆	22	J-533	PT+	−	+
	23	653	−	−	−
	24	Eaq	PT+	−	+

Exhibit J

	Slide	Section	MoAb				
	1	NK (Rico, Ronald)	J-4	J-5	+	+	
	2	"	J-14	J-96	+	+	
12	3	"	J-110	J-128	+	+	
	4	"	J-254	J-262	−	−	
	5	"	653	F31	−	+	
	6	NK liver (31-53291)	J-4	J-5	+	+	
	7	"	J-14	J-96	+	+	
3	8	"	J-110	J-128	+	+	
	9	"	J-254	J-262	−	−	
	10	"	653	[illegible]	−	+	
	11	PCA (Lee, Jian)	J-4	J-5	+	+	
	12	"	J-14	J-96	+	+	
	13	"	[illegible]	[illegible]	+	+	
3	14	"	[illegible]	[illegible]	−	−	
	15	"	653	Eq9	−	+	
V	16	NK, N.C. LN [illegible]	[illegible]	[illegible]	[illegible]	−	+
	17	"	J-662		+	−	+
	18	"	J-722		−	−	−
	19	"	J-791		+	+	+
	20	"	J-797		−	+	+
	21	"	[illegible]		−	−	−
	22	"	[illegible]		+	−	−
	23	"	J-816		+	+	+
	24	"	J-823		+	+	+
	25	"	653		−	−	−
	26	"	Eq9		P+	−	+

Exhibit K

	slide	Section	MoAb		Result	[redacted]
	1	NK (Rito, Rothalo)	J-415	J-533	PT+	PT+
12	2	"	653	Egg	—	PT+
35	3	Nor liver (31-53291)	J-415	J-533	—	—
	4	Nor Sm Intestine	J-415	J-533	—	—
44	5	(LAERANCE E)	653	W6/32	—	+
	6	Nor lung (20 II)	J-415	J-533	—	—
41	7	"	653	W6/32	—	+
	8	BpH (Krämmer A)	J-415	J-533	1-3+	1-2+
59	9	"	653	Egg	—	1-2+
59	10	CpH (Jseng, David	J-415	J-533	1-3+	1-2+
	11	"	653	Egg	—	1-3+
	12	PCa (Walsh, J	J-415	J-533	2-4+	2-4+
65	13	"	653	Egg	—	2-4+
	14	PCa (Linehan, E)	J-415	J-533	1-3+	1-3+
63	15	"	653	Egg	—	1-3+

Exhibit L

	Slide	Section	MoAb		Result	
	1	PCa	E455	E99	0-2+	0-2+
	2	(CANNON, THOMAS)	J-415	J-533	0-3+	0-3+
	3		J-591	653	0-3+	—
27	4		H125	H647	—	0-3+
	5		H648	H108-3	0-3+	0-1+
	6		P410	P30	1+	3+
	7	PCa	E455	E99	—	3+
	8	(CHEN, VEN)	J-415	J-533	3+	3+
	9		J-591	653	3+	—
27	10		H125	H647	—	1-3+
	11		H648	H108-3	1-3+	2+
	12		P410	P30	2+	3+
	13	PCa	E455	E99	3+	0-2+
	14	(LOPEZ, ALFORTUNADO)	J-415	J-533	1-2+	1-2+
	15		J-591	653	1-2+	—
27	16		H125	H647	0-3+	0-2+
	17		H648	H108-3	0-2+	0-1+
	18		P410	P30	1-2+	3+
	19	PCa	E455	E99	0-1+	1-2+
	20	(CHAN, YU CHING)	J-415	J-533	1-2+	1-2+
	21		J-591	653	1-2+	—
27	22		H125	H647	occasional 1+	3+
	23		H648	H108-3	3+	1+
	24		P410	P30	1-2+	3+
	25	PCa	E455	E99	4+	0-2+
	26	(O'BRIEN, WILLIAM)	J-415	J-533	0-3+	0-3+
27	27		J-591	653	0-2+	—
	28		H125	H647	0-3+	0-3+

Exhibit M

Publication Year: 2000

1329

Eradication of Prostate Cancer Xenografts by Immunoconjugates Targeting the Extracellular Domain of Prostate-Specific Membrane Antigen (PSMAext). *Lee Richstone, Daniel Yao, Sae Kim, He Liu, Ravi J Chari, Neil H Bander, Weill Medical Coll of Cornell Univ, New York, NY; ImmunoGen, Inc, Cambridge, MA.*

Introduction: We have developed a monoclonal antibody (mAb), J591, specific to $PSMA_{ext}$, which is rapidly internalized after binding (Liu *et al*, Can Res: 57:3629-3634,1997; ibid 58:4055-4060,1998). The parallel development of highly cytotoxic drugs, such as those of the maytansinoid class (with a 100- to 1000- fold greater cytotoxic potential than conventional chemotherapeutic agents), provides the opportunity for immunoconjugates effective against prostate cancer (Pca). We describe the use of mAb J591 for targeted delivery of the cytotoxic drug DM1 (a maytansine analog) to Pca cells. Methods: The mAb J591 was modified to introduce dithiopyridyl groups and conjugated to DM1 via a hindered disulfide bond. *In vitro*, LNCaP (PSMA-positive) and PC3 (PSMA-negative) human Pca cell lines were treated with varying doses of conjugate and dose-response curves were generated. *In vivo*, LNCaP and PC3 tumor xenografts were implanted subcutaneously in BALB/c nude mice. Once the xenografts reached a measurable size (7-10mm) treatment was initiated with unconjugated J591, unconjugated DM1, or conjugated J591-DM1 at varying doses: 100, 200, 300, or 400 mcg/day I.P. qd x 5. Tumor volume and animal weight (as a measure of toxicity) were closely followed. Results: *In vitro*, J591-DM1 had a ≥10-fold greater cytotoxicity against LNCaP vs. PC3 cells (IC_{50} 0.5 mcg/ml vs. IC_{50} ≥5 mcg/ml, respectively). *In vivo*, unconjugated J591 had no effect on LNCaP tumor volume. In contrast, LNCaP tumor volume was reduced in all mice treated with J591-DM1. A dose of 300mcg/day produced the greatest reduction in LNCaP tumor volume with minimal toxicity. At this dose, all eight animals had a major objective response. The tumors on half the animals had a > 50% shrinkage, and half had a complete response. Unconjugated DM1 at equimolar doses was lethal (100%) to the animals. PC3 tumor growth was not affected. Conclusions: The J591-DM1 immunoconjugate demonstrated effective, antigen-specific delivery of a highly cytotoxic drug to PSMA-positive Pca cells *in vitro* and *in vivo* with low systemic toxicity. Such an approach should be explored clinically.

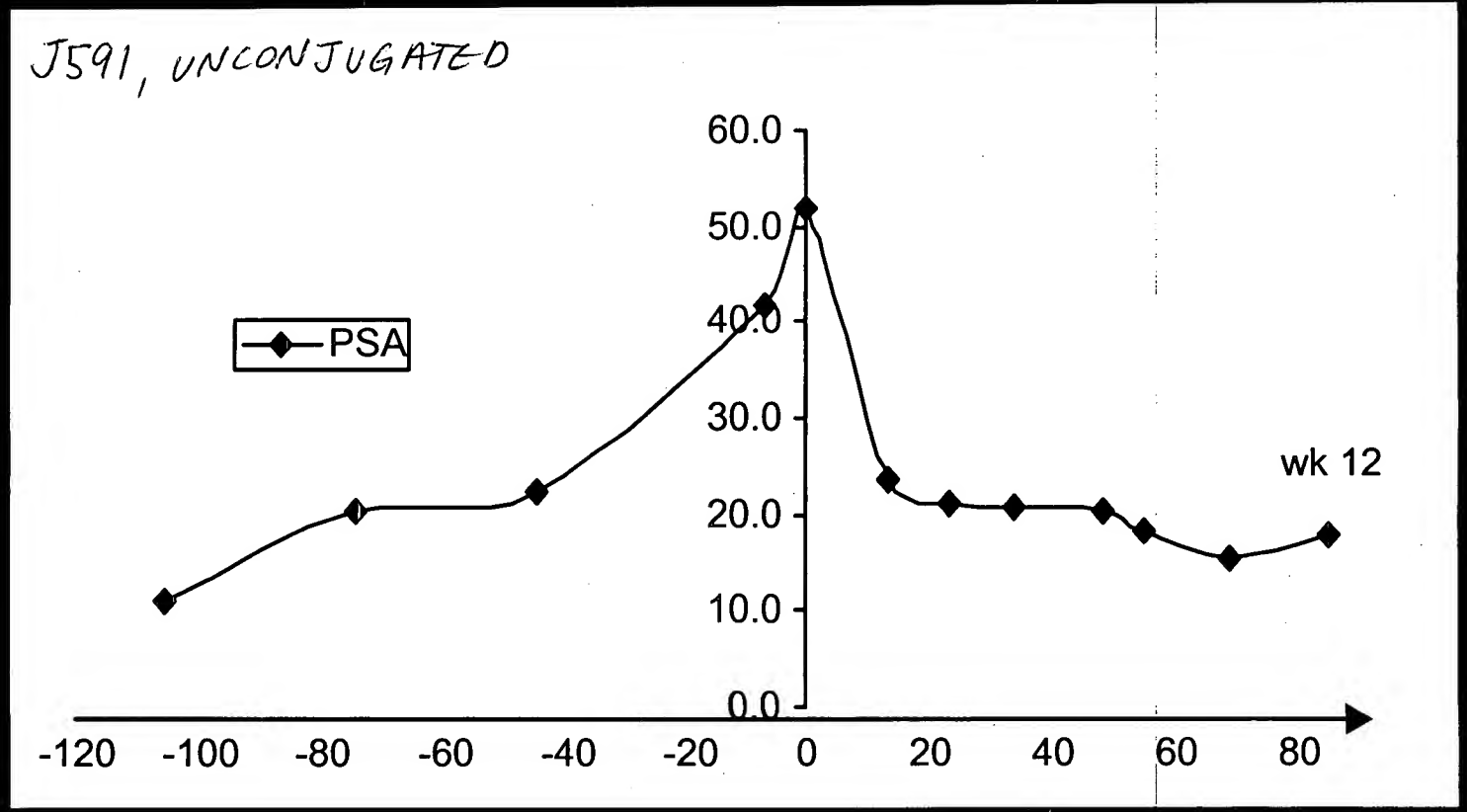
Exhibit N

PHASE I RADIOIMMUNOTHERAPY (RIT) TRIALS OF HUMANIZED MONOCLONAL (MAB) ANTIBODY J591 TO THE EXTRACELLULAR DOMAIN OF PROSTATE SPECIFIC MEMBRANE ANTIGEN ($PSMA_{EXT}$) RADIOLABELED WITH ^{90}YTTRIUM (90Y) OR ^{177}LEUTETIUM (^{177}LU) IN ADVANCED PROSTATE CANCER (PCA).

Neil H. Bander, Edouard J. Trabulsi, Daniel Yao, David Nanus, Maureen Joyce, Vincent Navarro, Sae Kim, He Liu, Julia Xia, Jaspreet S. Sandhu, Lalle Kostakoglu, Peter Smith-Jones, Shankar Vallabhajosula, Stanley Goldsmith. New York, New York.

Introduction and Objectives: J591 is a humanized mAb with specificity to $PSMA_{ext}$. It is the 1st mAb capable of binding PSMA on viable cells to enter clinical trials. The primary objectives of these Phase I RIT trials are to assess the targeting, toxicity, dosimetry, pharmacokinetics (PK), and immunogenicity of ^{90}Y- and ^{177}Lu-DOTA-J591 in patients (pts) with advanced Pca. As a secondary endpoint in these Phase I trials, anti-tumor responses were monitored. Methods: Eligible pts have progressing, metastatic, hormone-refractory Pca. To date, 26 pts have received ^{90}Y-J591 and 9 pts have received ^{177}Lu-J591. 1/3rd of the pts had failed at least one chemotherapy regimen. While ^{177}Lu can be imaged directly, ^{90}Y-J591 pts receive an initial dose of ^{111}In-J591, 1 week earlier, for imaging purposes. Dose levels are escalated in cohorts of 3-7 pts with a 6-8 week observation period between dose levels. Toxicity is evaluated and serum PK, dosimetry and human anti-humanized antibody (HAHA) reactivity are determined. Serum PSAs and measurable disease, when present, are followed. Results: 25 patients are evaluable. Virtually every known lesion was successfully targeted. Toxicity was dose-related and limited to reversible myelosuppression (primarily thrombocytopenia). MTDs are not yet defined. Current dose levels are: ^{90}Y=17.5 mCi/m^2; ^{177}Lu=30mCi/m^2. No patient has developed HAHA. Dose-related anti-tumor effects have been noted. 2 patients receiving ^{90}Y-J591 have had PSA declines of 65-85%. Both of these patients had measurable PRs. 1 patient receiving ^{177}Lu-J591, who did not have measurable disease, had a 50% PSA decline. All responses are durable at 3+ months. Conclusions: J591 targets tumor sites with sensitivity and specificity. The radiolabeled mAb is non-immunogenic. Toxicity has been limited to dose-related, reversible myelosuppression. J591 RIT induces dose-related anti-tumor effects in pts with advanced Pca. MTDs remain to be defined.

Exhibit O



Measurable response: PR